REMARKS/ARGUMENTS

Support for new claim 135 is provided at, *e.g.*, page 57, lines 3-6. Applicants have amended the description of Figure 5 in the brief description of the figures section of the specification. The description of SEQ ID 43 as the "proenzyme region" of SEQ ID NO: 2 has been amended to recite, "the active enzyme portion" of SEQ ID NO: 2. Support for this amendment is found at *e.g.*, p. 10, lines 22-24 of the specification. Applicants have also amended the cross-reference to related application section of the specification to conform with the initial ADS submitted herewith.

Objections

As requested by the Examiner, claim 78 has been amended: "Aβ" has been amended to recite "beta-amyloid (Aβ);" and, claim 84 has been amended: "APPsw" has been replaced with "amyloid precursor protein (Swedish mutation) (β-APPsw)."

Rejections

Rejection of Claims 81 and 82 Under 35 U.S.C. § 101

Claims 81 and 82 are rejected because they are allegedly directed to non-statutory subject matter. This rejection is respectfully traversed. It is the position of the Examiner that the scope of independent claim 81 and claim 82 depending therefrom includes use of a transgenic human being as a species in the genus of mammalian species comprising a transgene. Claim 81 has been amended to recite "excluding transgenic human beings" to expedite prosecution without conceding that the Examiner's rejection is warranted on this basis.

Rejection of Claims 78 and 81-83 Under 35 U.S.C. § 112, Second Paragraph

Independent claim 78 and claims 81-83 depending therefrom have been rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite, *i.e.*, the phrase "fewer than about 450" in claim 78 renders the claim indefinite. Without agreeing with the basis of the rejection, claim 78 has been amended to delete the phrase "fewer than about 450" to expedite prosecution.

Rejection of Claim 82 Under 35 U.S.C. § 112, First Paragraph: Lack of Written Description

Independent claim 82 is rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection. It is the position of the Examiner that neither the specification nor the claims identify characteristics of the transgene. Applicants respectfully point out that the specification does, in fact, identify the characteristics of the transgene, for example:

> "a transgene for human β-amyloid precursor protein (β-APP), such as a mouse bearing a transgene which encodes a human β-APP, including a mutant variants thereof, as exemplified in the specification."
> (*See* page 5, lines 24-30 of the specification).

Applicants also respectfully point out that the specification discuses rodent lines that express the human β-APP gene, for example:

> "[T]ransgenic animals predisposed to an amyloidogenic disease, such as various rodents bearing a human APP-containing transgene, *e.g.*, mice bearing a 717 mutation of APP described by Games et al., Nature 373: 523-527, 1995 and Wadsworth et al. (US 5,811,633, US 5,604,131, US 5,720,936), and mice bearing a Swedish mutation of APP such as described by McConlogue et al. (US 5,612,486) and Hsiao et al. (U.S 5,877,399); Staufenbiel et al., *Proc. Natl. Acad. Sci.* USA *94*, 13287-13292 (1997); Sturchler-Pierrat et al., *Proc. Natl. Acad. Sci. USA 94*, 13287-13292 (1997); Borchelt et al., *Neuron 19*, 939-945 (1997), all of which are incorporated herein by reference."

Lastly, originally filed claim 83, which depends from claim 82, recites "a mouse bearing a transgene which encodes a human β-amyloid precursor protein (β-APP), including a mutant variant thereof." Thus, both the specification and claims discuss identifying characteristics of the transgene.

Independent claim 82 has been amended to recite "a transgene which encodes a human β-amyloid precursor protein (β-APP), including a mutant variant thereof." This

amendment is made to expedite prosecution without conceding that the Examiner's rejection on this basis is warranted.

Rejection of Claims 78 and 81-85 Under 35 U.S.C. § 112, First Paragraph: Scope of Enablement

Claims 78 and 81-85 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled for *in vivo* testing. Applicants traverse this rejection.

It is the Examiner's position that claims 78 and 81-85 lack enablement because the specification fails to teach how to make a transgenic species comprising a human β-APP, teach ways of to administer the test compound, and to measure cognitive ability or plaque burden of subject mammals.

It is the Examiner's position that the specification fails to disclose the steps of claim 81, particularly, the way the test compound is administered, how to the cognitive abilities of the mammalian subject are measured, and how the plaque burden of the mammalian subject is measured. Applicants point to page 54, line 16 to page 55, line 3 of the specification which discusses the administration of test compounds, including the routes of administration, dose ranges, and methods well know in the art to determine routes of administration and dosage ranges. Measurement of the cognitive ability of mammalian subjects was well known in the art at the time of filing the instant application, *e.g.*, *see* pages 39-42 and Example 9 of WO/9640896. Measurement of plaque burden was also well known in the art at the time of filing the instant application, *e.g.*, *see* pages 51-52 and Example 6 of WO/9640896.

It is the Examiner's position that the specification fails to disclose the steps of claims 82 and 83, particularly, how to make a transgenic mammal, such as a mouse, that comprises the human β-APP gene. As discussed above, the specification teaches the characteristics of the transgene, *i.e.*, β-APP, and discusses transgenic rodent lines that express the human β-APP gene. Based on the foregoing, Applicants submit that no undue experimentation is required to practice the presently claimed invention and request that the rejection be withdrawn.

Rejection of Claims 78 and 81-85 Under 35 U.S.C. § 103(a) as Being Unpatentable Over WO 96/40885 and WO 9837226 Further In View of U.S. 6,319,689

Claims 78 and 81-85 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/40885 and WO 9837226 further in view of U.S. 6,319,689. The rejection is respectfully traversed.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors set out by *In re Vaeck*:

(1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and

(2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

In re Vaeck, 947 F.2d 448, 20 USPQ2d 1438 (Fed. Cir. 1991)

In re Royka sets out a third factor to be included in a proper analysis under § 103 It is well settled that a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). *See* also MPEP 2143.03.

It is the position of the Examiner that it would have been obvious to one having ordinary of skill in to modify the method disclosed in WO 96 40885 by using the purified β-secretase disclosed by Powell and the substrate of SEQ ID:83 as disclosed by WO 98/37226. Here the Examiner has failed to make a prima facie case because the cited references do not teach all of the elements of the claimed invention.

The Examiner asserts that WO 98/37226 and U.S. 6,319,689 provide the elements not discussed in WO 96/40885 and that it would have been obvious to modify WO 96/40885 to include such elements. It is the position of the Examiner that WO 96/40885 discloses a method for identifying β-secretase inhibitors and that the disclosed method determines β-secretase activity using one of the substrates of instant application, *i.e.*, SEQ ID NO: 104. The Examiner

states that WO 96/40885 does not disclose: (1) a β-secretase purified to apparent homogeneity; (2) substrate SEQ ID NO: 83 recited in claim 85; and, (3) the β-secretase recited in claim 78.

U.S. 6,319,689 does not disclose SEQ ID NO: 2 of the instant application. The Examiner asserts that U.S. 6,319,680 discloses the full amino acid sequence of SEQ ID NO: 2 of the instant application. Claims 78 and the claims depending therefrom recite the use of a protein purified to apparent homogeneity comprising a segment of a β-secretase enzyme protein wherein (i), the segment lacks the signal sequence (amino acid residues 1-22 with respect to SEQ ID NO:2) and the putative pro region (amino acid residues 23-45 with respect to SEQ ID NO:2). U.S. 6,319,689 does not disclose such a protein. The β-secretase enzyme protein recited in claim 78 is a protein having a valine at residue 130. U.S. 6,319,680 does not disclose such an amino acid sequence. Applicants respectfully point out that the SEQ ID NO: 2 disclosed in the instant application differs from SEQ ID NO: 2 disclosed by U.S. 6,319,680 at amino acid 130. The instant application discloses a valine residue at position 130, while U.S. 6,319,680 discloses an glutamic acid residue at position 130. (*See* Exhibit 1, attached hereto,) The failure of U.S. 6,319,680 to teach SEQ ID NO: 2 of the present application precludes anticipation of SEQ ID NO: 2 of the instant application based on this reference. Since none of the cited references, WO 96/40885, WO 98/37226, and U.S. 6,319,689, teach the β-secretase used in the methods of the presently claimed invention, there is no *prima facie* case of obviousness.

The cited references do not suggest or provide the motivation to modify the cited references to result in the presently claimed invention. It is the position of the Examiner that it would have been obvious to one having ordinary of skill in to modify the method disclosed in WO 96/40885 by using the purified β-secretase disclosed by U.S. 6,319,680 and the substrate of SEQ ID:83 as disclosed by WO 98/37226. As discussed above, U.S. 6,319,680 does not teach SEQ ID NO: 2 of the present application. The Examiner has provided no suggestion or motivation for those of ordinary skill to modify the sequence disclosed by U.S. 6,319,680.

Based on the foregoing Applicants request the rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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